Applicant respectfully disagrees with the conclusions the Examiner has drawn for the following reasons:

(i) The Specification itself provides evidence that the disclosed mouse and human LOBO proteins are functional homologs. In particular, the application discloses that the identified mouse and human genes are localized on syntenic chromosomal regions (see Example 4 on page 27 and the paragraph bridging pages 10 and 11). This means that the murine gene is located on chromosome 1 in band 1D, a locus which corresponds to human chromosome 2, region 2q35-37, exactly the region where the human LOBO gene has been mapped.

(ii) The cDNA encoding the human LOBO protein and the cDNA encoding the mouse LOBO protein share a sequence homology of 85.2% (see Appendix II attached to the Declaration of Dr. Andreas Rump). The encoded proteins share a homology of 88.1% (see Appendix I attached to the Declaration of Dr. Andreas Rump). Given that many amino acid changes are conserved (e.g. Lys-Arg, Glu-Asp, Leu-Ile, etc.), the similarity between the two proteins is actually even higher. These high levels of sequence identity on the nucleotide and the amino acid level between mouse and human is a further strong indication that the human protein disclosed in the present application is indeed the functional analog of the mouse LOBO protein.

(iii) The inventors have produced antibodies against the recombinantly produced mouse LOBO protein disclosed in the present application. These antibodies also recognize the human LOBO protein of the present invention. These cross-reactivities are a very strong indication that the proteins are highly conserved and, thus, also exert the same function.

(iv) The inventors have shown the both the mouse and the human LOBO protein disclosed in the present application are specifically localized in the cytosol of the cell.

(v) Glycerol-gradient centrifugation experiments have shown that both the human and mouse LOBO proteins described in the present application are present in a high molecular weight complex.

The foregoing remarks clearly show that the human LOBO protein disclosed in the present application is the functional homologue of the mouse LOBO protein and, thus, also fulfills the functional requirement of claim 1. This means that the human and mouse LOBO protein do have a common "special technical feature" which establishes that there is indeed unity of invention under PCT Rule 13.1. It does not appear from the outstanding Office Action that the Examiner has even considered the restriction requirement under the standard of PCT Rule 13.1. This represents a clear error in the Examiner's analysis. Accordingly, Applicant respectfully requests reconsideration and removal of the restriction requirement.

Please note that Applicant has added new claim 36 directed to the elected species.

2. Drawings

The drawings have been objected to for reasons set forth in PTO-948. The draftsperson had indicated that Figures 1, 4, 7 and 8 were of poor quality. The draftsperson also indicated that Figures 1-10 were unacceptable because of visible copy machine marks. The draftsperson also indicated that the character of lines, numbers and letters in certain of the figures were poor. Applicant hereby submits a new set of drawings. Reconsideration and removal of the objection is respectfully requested.

3. Specification

The Examiner has objected to the Specification because the description of Figures 2 and 3 does not correspond to the figures. The Examiner also notes that the description on page 24 describing the cloning and sequencing of the murine genomic sequences makes reference to SEQ ID NOs associated with the human sequences. Applicant has amended the Specification to correct the description of the figures. Applicant has also amended the description on page 24 to remove the reference to the human sequences and substitute the appropriate murine SEQ ID Nos. Reconsideration and removal of the objections is respectfully requested.

4. Claim Objections

Claims 8, 12 and 13 were objected to for being improper multiple dependent claims. Specifically, the Examiner noted that the claim 8 referred to both claims 1 and 7 but not alternatively. Claims 12 and 13 were objectionable because of the use of the term "and/or". Applicant has amended the claims to comply with proper U.S. format. Reconsideration and removal of the objections are respectfully requested.

5. Rejections under 35 U.S.C. § 101 and §112

The Examiner has rejected claims 1, 2 and 4 for being directed to non-statutory subject matter because the claims are not directed to an isolated nucleic acid molecule and therefore read on nucleic acid molecules that exist in a living mouse. Applicant has amended the claims in accordance with the Examiner's suggestion to overcome the rejection.

The Examiner has also rejected claims 1-7, 20, 21 and 23-26 under 35 U.S.C. § 101 (and under 35 U.S.C. § 112, first paragraph for lack of enablement) because the claimed invention "is not supported by either a specific and substantial asserted utility or a well established utility". Applicant respectfully disagrees. The Examiner asserts that the Specification does not identify a single disease, including one involving bone growth and development, that could either be diagnosed or treated with a nucleic acid molecule of the invention. Applicant respectfully disagrees. The Specification discloses that the LOBO proteins are involved in mitosis and cell cycle, as well as, human growth disorders not caused by nutrition or hormones (see page 7). Page 1 identifies several growth diseases that may be treated using the present invention. Example 7 also discusses the connection between the LOBO protein and AHO. Applicant would also like to direct the Examiner's attention to the second to last paragraph on page 14, which discusses the use of the LOBO gene/protein in the treatment of diseases or disorders which involve growth disturbance (e.g., growth disturbance relating to bones). Such growth disturbances are mentioned on page 1, second paragraph, and include achondroplasia. Achondroplasia is a disease, which is, *inter alia*, characterized by stunted growth (due to too short bones) except for the skull which is not affected. It is the most common form of human dwarfism and is a consequence of inefficient proliferation of chrondrocytic progenitors. This is

the exact opposite of the phenotype of the LOBO mutation described in the present application. A person of ordinary skill in the art reading the present application would immediately realize that, based on the data provided on transgenic mice, such a disease may be ameliorated by reducing or inhibiting the expression of the LOBO gene disclosed in the present application. Methods of achieving such a reduction or inhibition are disclosed in the application (e.g. on page 15, second paragraph).

Furthermore, the present application demonstrates that the exaggerated bone growth of the LOBO mouse is histologically reflected in a thickened growth zone (proliferative zone) of the bones. Moreover, an increase in the number of hypertrophic chondrocytes in the growth zone is observed (see Figure 4 and legend on page 16 and Example 1 on page 21). This clearly indicates to the skilled person that the LOBO gene may be employed in order to perform cartilage tissue engineering with mesenchymal/embryonic stem cells. In particular, it is obvious to a person of ordinary skill that mesenchymal/embryonic stem cells genetically modified as described in the LOBO mouse can, e.g., be used to produce cartilage substitutes or tissue substitutes for medical applications. Another obvious field of application is the use in injury related bone fracture healing. This process involves an intermediate chondrogenic step, which could be affected by the LOBO protein.

The foregoing remarks demonstrate the various utilities of the present invention. The utilities discussed above are specific, substantial and credible and would be apparent to a person of ordinary skill in the art after reading the Specification. Applicant further submits that a person skilled in the art would know how to use the claimed invention. As such, Applicant submits that the Specification meets the utility requirements of 35 U.S.C. § 101 and the enablement requirement under 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and removal of the rejection is respectfully requested.

6. Written Description

Claims 1-7, 20, 21 and 23-26 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way to reasonably convey to a person of ordinary skill in the art that the inventors were in possession of

the invention at the time the application was filed. The Examiner acknowledges that the application describes one protein, the murine LOBO protein, which meets the requirements of the claim (i.e. by disclosing the nucleic acid sequence encoding SEQ ID NO. 9). However, the Examiner argues that the Applicant is not entitled to a generic claim directed to the murine LOBO protein and any generic nucleic acid sequence whose complement hybridizes to a sequence encoding murine LOBO and encodes a protein, the reduction or inactivation of which in an animal causes bones, except for the skull, to become longer. Specifically, the Examiner alleges that the Applicant has only disclosed a partial amino acid sequence for the human homolog of murine LOBO (SEQ ID NO. 14) and has failed to demonstrate that it meets the phenotypic limitation of the claim. Moreover, the Examiner argues that the disclosure that other eurkaryotic DIS3 proteins, VACB and RNAase II proteins of bacteria and fungi, as well as a LOBO homolog of *C. elegans* which are homologous to the LOBO protein and yet do not meet phenotypic limitation clearly demonstrates the lack of written description support for the broad genus claim. Applicant respectfully disagrees. The Specification provides clear support for nucleic acid sequences whose complement hybridizes to a sequence encoding murine LOBO which meets the phenotypic limitation of the claim as recited in new claim 41. The Examiner's attention is directed to pages 7-10 of the Specification.

The written description requirement requires the inventor to clearly convey to those skilled in the art through the Specification the information that applicant has invented the specific subject matter of the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Applicants submit that they have met this requirement. Pages 6 and 7 of the application describe the relationship amongst the various proteins noted above and the correlation between the structure of the protein and the expected function. As such, Applicants submit that they are entitled to the broad scope of the claim.

With respect to the Examiner's comments regarding the human homolog of the murine LOBO protein and its expected function, Applicants offer the following comments:

The application demonstrates that the reduction or inactivation of the murine LOBO protein in mice causes bones, except for skull bones, to become longer. The Examiner asserts that Applicants have failed to demonstrate that the human homolog of murine LOBO meets the

phenotypic limitation of the claim. Obviously, Applicant cannot be required to include human test data to support their hypothesis. To determine whether the application provides sufficient written description support for the claims, one must inquire whether one skilled in the art can reasonably conclude that the inventor was in possession of the claimed invention. In the instant case, this issue is whether the application demonstrates the connection between the human and murine LOBO proteins and their expected function. Applicants believe that the application supports such a finding.

As discussed in Example 7 of the Specification, it would be reasonable to believe that the inactivation or the reduction of the human LOBO protein could be used in the treatment of AHO (Albright Hereditary Osteodystrophy), a disease characterized by hyposomia and brachydactylia (short fingers). Although Applicants concede that the symptoms of AHO may vary from patient to patient, it is entirely reasonable for a person of ordinary skill in the art to conclude that the inactivation or reduction of the human LOBO protein could be used to treat AHO (or symptoms of AHO), in particular, brachydactylia, based upon (1) the data presented in the application with respect to the effect of murine LOBO in mice and (2) the similarity in the structure of the human and murine LOBO proteins and the likelihood of similar function of the LOBO protein in humans.

As noted by the Examiner, Applicants have provided the sequence for the murine LOBO protein and a sequence for the human homolog of the murine LOBO protein. Page 6 of the Specification also discusses the relationship between the murine and human LOBO proteins (see the second full paragraph). The function of the human and murine LOBO proteins and the VacB-, RNAaseII and Dis3 proteins is discussed on page 7. Although human and murine LOBO proteins also share some relationship to the VacB, RNAase II and Dis3 protein, the inventors specifically state that the murine and human LOBO proteins constitute a "group of their own". The close relationship between the murine and human LOBO proteins is illustrated in Fig. 3, which shows the sequence comparison between the two and is also highlighted on pages 10-11 of the Specification which describes the chromosomal location of the human and murine LOBO gene. For the Examiner's convenience, Applicants have also enclosed a printout, which more clearly depicts the protein alignment of the mouse v. human LOBO as of Applicant's filing date (see Appendix I attached to the Declaration of Dr. Andreas Rump). Given the disclosure in the

Specification and the high degree of conservation between the human and murine LOBO proteins (88% sequence identity on the amino acid level and 85% sequence identity on the nucleotide level), it would be entirely reasonable for a person of ordinary skill in the art to conclude that the human and murine LOBO proteins would share the same function. This is especially true as mice and men are both highly developed and closely related mammals.

The foregoing remarks clearly demonstrate that the human and murine LOBO proteins can be considered functional analogs. Accordingly, Applicants submit that they are at least entitled to claims that would encompass the human and murine LOBO proteins. Applicants further submit that they are entitled to claims, which would encompass proteins that share at least a 70% homology with the human and murine LOBO proteins as recited in amended claim 1. As noted on page 9 of the Specification, proteins having a percent homology of at least 70% would be expected to share the same functional and/or structural equivalence to the human and murine LOBO proteins. Applicants have conducted BLAST searches of the GenBank database using the entire sequence of the mouse LOBO sequence. The results summarized in the attached Declaration, demonstrates that, as of Applicant's filing date, no sequences existed with more than 70% sequence identity. Likewise, Applicants submit that claims 37-40 are similarly supported by the search results and the Specification (see page 9).

Reconsideration and removal of the written description rejection is, therefore, respectfully requested.

7. Rejections under 35 U.S.C. §102(b)

Claims 1, 2, 4 and 7 have been rejected as anticipated by Browning et al. Applicants believe the foregoing claim amendments suggested by the Examiner have obviated the anticipation rejection. Reconsideration and removal of the rejection is respectfully requested.

Favorable action and early allowance of the claims are requested.

If the Examiner has any questions concerning this application, he is requested to contact Leonard Svensson (Reg. No.: 30,330) the undersigned at (714) 708-8555 in the Southern California area.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $465.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on: March 3 2003
(Date of deposit)

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Susan M. Dougherty
(Signature)

March 3 2003
(Date of Signature)

Respectfully submitted,

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Attachments: Version of the Claims With Markings to Show Changes Made
Specification with Markings to Show Changes Made
Declaration under 37 C.F.R. §1.132 of Dr. Andreas Rump w/ Appendix I, Appendix II, Table 1 and Table 2
Drawings

VERSION OF THE CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences encoding the amino acid sequence depicted in SEQ ID No. 9 or in SEQ ID No. 14;

(b) nucleic acid sequences depicted in SEQ ID No. 8 or SEQ ID No. 13;

(c) [nucleic acid sequences, the complementary sequence of which hybridizes to the sequences mentioned in (a) or (b)] nucleic acid molecules encoding a protein, the amino acid sequence of which has a homology of at least 70% to the amino acid sequence of SEQ ID No. 9 or SEQ ID No. 14 ; and

(d) nucleic acid sequences deviating from the sequences mentioned in (c) on account of the degeneracy of the genetic code,

wherein the nucleic acid molecule encodes a protein, the reduction and/or inactivation of which in animals results in [that] the elongation of the bones, with the [except for] exception of the [scull] skull bones [become].

2. (Amended) The isolated nucleic acid molecule according to claim 1, which is genomic DNA.

4. (Amended) The isolated nucleic acid molecule according to claim 1, which is an RNA molecule.

7. (Twice Amended) A host cell transformed by an isolated nucleic acid molecule according to any one of claims 1 to 4.

8. (Amended) A method for preparing a protein which is encoded by a nucleic acid molecule according to claim 1, wherein a host cell [according to claim 7] is cultured under

conditions permitting the expression of the protein and the protein is recovered from the cells and/or the culture medium.

12. (Twice Amended) A diagnostic composition containing a nucleic acid molecule according to any one of claims 1 to 4[, a protein according to claim 9, an antibody according to claim 10 and/or a nucleic acid molecule according to claim 11].

13. (Twice Amended) A pharmaceutical composition containing a nucleic acid molecule according to any one of claims 1 to 4 [, a vector according to claim 5 or 6, a protein according to claim 9, an antibody according to claim 10 and/or a nucleic acid molecule according to claim 11] and optionally a pharmaceutically acceptable carrier.

SPECIFICATION WITH MARKINGS TO SHOW CHANGES MADE

On page 16, please replace the paragraph describing Figure 2 with the following:

--[Figure 2]Figure 2a-2m [shows the first pursued sequencing strategy for sequencing the murine and human LOBO gene (SEQ ID NOS: 24-34). As at first only the 3'-end of the gene was sequenced, the exons starting at the 3'-end were numbered 1, 2, 3 etc. Three murine wildtype cosmid clones (middle) were sequences, two plasmid clones were sequences from the transgenic LOBO mouse (top) and a human P1-clone (bottom) was sequenced. The arrows denote the exons known for the time being. Seven exons were located on the genomic sequence, the eighth exon at first only existed on an EST clone. The plasmid clones from the transgenic LOBO mouse (top) contain the introduced artificial gene and the adjacent murine sequences. These murine sequences are identical to the corresponding sequences of the wildtype mouse except for 10 base pairs, which have been replaced in the transgenic mouse by the artificial gene] shows a sequence comparison between the human (HS) and murine (MM) LOBO proteins and the eukaryotic Dis3-homologous and Dis3-type proteins .--

On page 16, please replace the paragraph describing Figure 3 with the following:

--Figure 3 [shows a sequence comparison between the human (HS) and murine (MM) LOBO proteins and the eukaryotic Dis3-homologous and Dis3-type proteins] shows the first pursued sequencing strategy for sequencing the murine and human LOBO gene (SEQ ID NOS: 24-34). As at first only the 3'-end of the gene was sequenced, the exons starting at the 3'-end were numbered 1, 2, 3 etc. Three murine wildtype cosmid clones (middle) were sequences, two plasmid clones were sequences from the transgenic LOBO mouse (top) and a human P1-clone (bottom) was sequenced. The arrows denote the exons known for the time being.

Seven exons were located on the genomic sequence, the eighth exon at first only existed on an EST clone. The plasmid clones from the transgenic LOBO mouse (top) contain the introduced artificial gene and the adjacent murine sequences. These murine sequences are identical to the corresponding sequences of the wildtype mouse except for 10 base pairs, which have been replaced in the transgenic mouse by the artificial gene.--

Please replace the first full paragraph on page 24 with the following:

--The open reading frame starts at position 8520 in SEQ ID NO: 5. The stop codon is located at position 18202 in SEQ ID NO: 6. The coding region encodes the amino acid sequence depicted in SEQ ID NO: 2. A detailed computer analysis of the first obtained sequence data led to the identification of a gene which consists of at least 8 coding sections ("exons"). The first identified coding region which is depicted in SEQ ID NO: 1 carries the information for the 393 amino acids. An overview of the sequences murine clones obtained in the subsequent sequencing of the 138 kb region is schematically depicted in Figure 10. The sequenced region comprises altogether 138884 base pairs (see SEQ ID NOS: 10-12 [12-15]) and contains 12 exons. The exons are localized at the following positions:--